# Prevention

## Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine

The mRNA-1273 vaccine is a mRNA-based vaccine that encodes the pre-fusion stabilised full-length spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A recent phase 3 randomised, placebo-controlled randomised trial was completed at 99 centers across the United States. People at high risk for SARS-CoV-2 infection or its complications were to receive two injections of mRNA-1273 (100 µg) or placebo 28 days apart. The primary outcome was prevention of COVID-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2. The recruited 30,420 volunteers were assigned to receive either vaccine or placebo (15,210 participants in each group). Symptomatic COVID-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the vaccine group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across important secondary analyses. 30 participants developed severe COVID-19, with one death; they were all in the placebo group. Serious adverse events were rare, and equally distributed in both groups.

Baden LR, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020 Dec 30. doi: 10.1056/NEJMoa2035389. Epub ahead of print. PMID: 33378609.

## Does HPV vaccination reduce the risk of invasive cervical cancer?

Human papillomavirus (HPV) vaccination is known to prevent HPV infection and associated high grade pre-cancerous lesions. Whether vaccination is also associated with a subsequently lower risk of invasive cervical cancer is not well studied. Using nationwide Swedish demographic and health registers, 1,672,983 girls and women who were 10 to 30 years of age were followed from 2006 through 2017; and the association between HPV vaccination and the risk of invasive cervical cancer was assessed. Cervical cancer was diagnosed in 19 women who had received the HPV compared to 538 women who had not received the vaccine. The cumulative incidence of cervical cancer was significantly lower among women who had been vaccinated compared to those who were not; 47 cases per 100,000 persons versus 94 cases per 100,000 persons, respectively. It was concluded that among Swedish girls and women 10 to 30 years old, HPV vaccination was associated with a ssignificantly lower risk of invasive cervical cancer at the population level.

Lei J, Ploner A, Elfström KM, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. doi: 10.1056/NEJMoa1917338. PMID: 32997908.

## Immunogenicity and fractional doses of yellow fever vaccines

Available stock of yellow fever vaccine does not meet the demands for outbreak response. Fractional dosing is efficacious but the available evidence is limited to the 17DD substrain vaccine. Researchers, through a non-inferiority trial with centers in Uganda and Kenya, evaluated the immunogenicity and safety of one-fifth fractional dose compared with standard dosing of four WHO-prequalified yellow fever vaccines produced from three substrains. The primary outcome was proportion of participants with seroconversion 28 days after vaccination. 960 participants were enrolled; 900 were included in the per-protocol analysis and 959 in the safety analysis. Fractional doses from all four vaccines met the predefined non-inferiority criterion. The most common treatment-related adverse events were headache (22·2%), fatigue (13·7%), myalgia (13·3%) and self-reported fever (9·0%). “Fractional doses of all WHO-prequalified yellow fever vaccines were non-inferior to the standard dose in inducing seroconversion 28 days after vaccination, with no major safety concerns. These results support the use of fractional dosage in the general adult population for outbreak response in situations of vaccine shortage” the authors concluded.

Juan-Giner A, et al. Immunogenicity and safety of fractional doses of yellow fever vaccines: a randomised, double-blind, non-inferiority trial. Lancet. 2021 Jan 9;397(10269):119-127. doi: 10.1016/S0140-6736(20)32520-4.

## Polypill with or without Aspirin for prevention of cardiovascular disease

Use of pharmacological interventions for primary prevention of cardiovascular disease is a growing area for research. In a recent randomised trial with a factorial design researchers tested whether treatment with a polypill containing a statin and multiple blood-pressure–lowering drugs, aspirin alone, or their combination would reduce the incidence of cardiovascular events among persons with intermediate cardiovascular risk but without cardiovascular disease. A total of 5713 participants were followed up for 4.6years. They found that the polypill combined with Aspirin significantly reduced the risk of cardiovascular events (hazard ratio, 0.69; CI, 0.50 to 0.97) but the reductions in cardiovascular events from the polypill alone and from aspirin alone were not statistically significant. From the study, it was concluded that combined treatment with a polypill plus aspirin led to a lower incidence of cardiovascular events than did placebo among participants without cardiovascular disease who were at intermediate cardiovascular risk.

Yusuf, S. et al. Polypill with or without aspirin in persons without cardiovascular disease. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa2028220 (2020)

## Hydroxychloroquine for prevention of COVID-19 infection

With the increasing urgent need for pharmacological interventions for prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, studies on the role of hydroxychloroquine have continued despite previous negative findings. A recent large open-label cluster-randomised trial involving 2314 asymptomatic contacts of 672 index patients with polymerase-chain-reaction (PCR)–confirmed COVID-19 in Spain, was added to the existing evidence. A total of 1116 contacts were randomly assigned to receive hydroxychloroquine and 1198 to receive usual care. The incidence of PCR-confirmed and symptomatic COVID-19 was similar in both study groups (risk ratio, 0.86 [95% confidence interval, 0.52 to 1.42). Hydroxychloroquine was however, associated with a significantly higher risk of adverse events compared

to usual care (56.1% vs. 5.9%). In conclusion, the study found no benefit of postexposure therapy with hydroxychloroquine in prevention of SARS-CoV-2 infection or symptomatic COVID-19 in healthy persons exposed to a PCR-positive patient.

Mitjà et al. (Nov 24, 2020). A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of COVID-19. New England Journal of Medicine. https://doi.org/10.1056/NEJMoa2021801

# COVID-19

## Real-life validation of the PanbioTM COVID-19 antigen rapid test

Reverse transcriptase Polymerase Chain Reaction (RT-qPCR) the reference test for diagnosis of SARS-CoV-2 infection is associated with undesirable diagnostic delays. Antigen based tests are quicker and can be performed outside of laboratory but their performance in real life settings have not been well studied. In a recent study the diagnostic value of the PanbioTM COVID-19 Ag Rapid Test (Abbott), was compared with RT-qPCR in mildly symptomatic patients at two community-based testing centers (University Medical Center Utrecht in the Netherlands and the HoracioOduber Hospital on Aruba). 1367 and 208 subjects were enrolled in Utrecht and Aruba, respectively. SARS-CoV-2 prevalence, based on RT-qPCR, was 10.2% (n = 139) and 30.3% (n = 63) in Utrecht and Aruba respectively. Specificity was 100% (95%CI: 99.7_100%) in both settings. Test sensitivity was 72.6% (95%CI: 64.5_79.9%) in the Netherlands and 81.0% (95% CI: 69.0_89.8%) in Aruba. The authors concluded that given the sensitivity and specificity, the short turnaround times, user friendliness, low cost and opportunities for decentralised testing, the test could improve efforts towards transmission.

H. Gremmels et al., Real-life validation of the PanbioTMCOVID-19 antigen rapid test (Abbott) in community-dwellingsubjects with symptoms of potential SARS-CoV-2 infection, EClinicalMedicine (2020)

## Antibody responses after asymptomatic or mild SARS-CoV-2 Infection

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection elicits an antibody response among both asymptomatic and symptomatic people, with a stronger initial response among those with more severe disease. The waning nature of this immunity is still being studied and the findings are variable. A recent study in South Korea assessed the antibody responses of 58 people with confirmed asymptomatic or mildly symptomatic SARS-CoV-2 infection 8 months after diagnosis. Three of the four assays used showed high seropositivity rates (69% to 91.4%; $P < 0.01$). These findings contrast earlier studies that have reported a shorter antibody lifespan in this category of patients. The authors suggest variations in immunoassay test characteristics as possible explanations for the varied findings. They concluded that "Despite concerns of waning immunity, appropriate immunoassays can detect antibodies against SARS-CoV-2 at 8 months after infection in most asymptomatic or mildly symptomatic persons".

Choe PG, et al. Antibody responses 8 months after asymptomatic or mild SARS-CoV-2 infection. Emerg Infect Dis. 2021 Mar [date cited]. https://doi.org/10.3201/eid2703.204543 Original Publication Date: December 22, 2020

## A randomised trial of convalescent plasma in COVID-19 severe pneumonia

In this heat of the COVID-19 pandemic, various therapies continue to be used and evaluated often, simultaneously. Convalescent plasma has been used in patients with COVID-19 largely based on observational data. A total of 333 hospitalised adult patients with severe COVID-19 pneumonia were randomly assigned in a 2:1 ratio to receive convalescent plasma or placebo. The primary outcome was the patient's clinical status 30 days after the intervention, as measured on a six-point ordinal scale ranging from total recovery to death. At 30 days, no significant difference in the distribution of clinical outcomes according to the ordinal scale was noted between the convalescent plasma group and the placebo, while mortality was 10.96% and 11.43% respectively. It was concluded that there were no significant differences observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo.

Simonovich VA, Burgos Pratx LD, et al. A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia. The New England Journal of Medicine. 2020 Nov. DOI: 10.1056/nejmoa2031304.

## Treatment duration with Remdesivir for patients with Severe COVID-19

Remdesivir, an RNA polymerase inhibitor with potent antiviral activity in animal models of COVID-19, has been used in research settings to treat patients with COVID-19. In a recent multicenter, randomised phase 3 trial researchers treated patients with confirmed severe SARS-CoV-2 infection, who did not require intubation and had radiologic evidence of pneumonia with Remdesivir. They assigned patients to receive Remdesvir for 5 days or for 10days and compared their clinical status on day 14, as assessed on a 7-point ordinal scale. After adjusting for baseline clinical status, they found that patients in the 10-day and 5-day groups had a similar distribution in clinical status at day 14. It was concluded from the study that there was no significant difference between a 5-day and a 10-day course of remdesivir, in patients with severe COVID-19 not requiring mechanical ventilation.

Goldman JD, Lye DCB, et al. Remdesivir for 5 or 10 Days in Patients with Severe COVID-19. N Engl J Med. 2020 Nov 5;383(19):1827-1837. doi: 10.1056/NEJMoa2015301. Epub 2020 May 27. PMID: 32459919; PMCID: PMC7377062.

## Repurposed antiviral drugs for COVID-19 — interim WHO solidarity trial results

This World Health Organization sponsored study evaluated the effect of four repurposed antiviral drugs: Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon beta-1a, on COVID-19 related mortality. The trial recruited 11,330 adults in 30 countries. COVID-19 in-patients were randomly assigned equally between one of the trial drugs that was locally available and open control (up to five options, four active and the local standard of care). No drug was shown to reduce mortality, reduce initiation of ventilation or hospitalisation duration; as deaths occurred in 301 of 2743 patients receiving remdesivir and in 303 of 2708 receiving its control, in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving the control, in 148 of 1399 patients receiving lopinavir and in 146 of 1372 receiving its control, and in 243 of 2050 patients receiving interferon and in 216 of 2050 receiving its control. It was concluded that these drugs had little or no effect on overall mortality, initiation of

ventilation, and duration of hospital stay among hospitalised patients with COVID-19.

WHO Solidarity Trial Consortium, Pan H,et al. Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2020 Dec 2:NEJMoa2023184. doi: 10.1056/NEJMoa2023184.

# MCH

## Antenatal dexamethasone for early preterm birth in low-resource countries

Antenatal glucocorticoids have been identified as a key intervention for reducing preterm morbidity and mortality based on trials conducted in high-resource countries. Evidence on their safety and efficacy in low-resource settings is controversial. The World Health Organization (WHO) sponsored a multi-center placebo-controlled randomised trial on the safety and efficacy of intramuscular dexamethasone, involving 2,852 pregnant women at risk for imminent preterm birth from 29 hospitals across Bangladesh, India, Kenya, Nigeria, and Pakistan. The primary outcomes were neonatal death alone, stillbirth or neonatal death, and possible maternal bacterial infection. The trial was stopped for benefit at the second interim analysis. The frequency of neonatal death was significantly lower in the dexamethasone group compared to the placebo group (RR 0.84; P=0.03). Findings for stillbirth or neonatal death were similar (RR 0.88; P=0.04). There was no significant difference in the rates of maternal bacterial infection or adverse events.

WHO ACTION Trials Collaborators, Oladapo, et al. (2020). Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries. The New England journal of medicine, 383(26), 2514–2525. https://doi.org/10.1056/NEJMoa2022398

## Causes of infertility in women presenting to gynaecology clinics

Infertility, defined clinically as failure to conceive after 12 months or more of regular unprotected sexual intercourse, is an important condition, affecting 48.5 million couples globally. The contribution of various aetiological factors to infertility differs with different populations. Researchers in Harare, Zimbabwe recently conducted a survey among 216 women. Two thirds (144) of them had primary infertility. The most common cause for infertility was 'unexplained' in 22% of the women followed by tubal blockage in 20%, male factor in 19% and anovulation in 16%. The overall period of infertility ranged from 1 to 21 years with an average of 5.6 ± 4.7 years. 98 (45.4%) of the couples had experienced 2–4 years of infertility and 94 (43.5%) had experienced 5 or more years of infertility. The study found that most women present when chances of natural spontaneous conception are considerably reduced and that previously enumerated causes; tubal blockage, male factors and unexplained infertility contributed equally.

Madziyire, M.G., et al. The causes of infertility in women presenting to gynaecology clinics in Harare, Zimbabwe; a cross sectional study. Fertil Res and Pract 7, 1 (2021). https://doi.org/10.1186/s40738-020-00093-0

## A review of the psychosocial impact of fibroids before and after treatment

Despite a high prevalence of uterine fibroids, their psychosocial impact has not been adequately evaluated. In a recent review that included 57 studies, the quality of life scores of premenopausal women with fibroids were reviewed at baseline and compared with those of published quality of life scores in other disease populations in addition to after fibroid treatment. They found a diagnosis of uterine fibroids had a disability score similar to or exceeding (was a greater psychosocial stressor) that of heart disease, diabetes mellitus, or breast cancer. Uterine fibroids were associated with significant patient-reported health disabilities linked with bodily pain, mental health, social functioning, and sexual satisfaction. Validated quality of life instruments indicated therapeutic success and the improvement of both physical and emotional symptoms after treatment.

Virginia Arlene A. Go, et al. A systematic review of the psychosocial impact of fibroids before and after treatment, American Journal of Obstetrics and Gynecology, https://doi.org/10.1016/j.ajog.2020.05.044.

## Diagnosis and treatment of vaginal discharge syndromes in community practice settings

Although vaginal discharge symptoms are common, diagnosis of common causative agents including; bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and Trichomonas vaginalis (TV) is not standardised. Diagnostic approaches and appropriateness of treatment were evaluated for women with symptoms of vaginitis who were seeking care at community practice sites. Of the 170 women having a laboratory-diagnosed cause of vaginitis, 81 (47%) received 1 or more inappropriate prescriptions. Of the 120 women without BV, TV, or VVC, 41 (34%) were prescribed antibiotics and/or antifungals. Among women without infectious vaginitis, return visits for vaginitis symptoms were more common among women treated empirically compared to those who did not receive treatment (9/41 vs 5/79, P = .02). The researchers concluded that in a community practice setting, 42% of women with vaginitis symptoms received inappropriate treatment. Women without infections who received empiric treatment were more likely to have recurrent visits within 90 days.

Sharon L Hillier, Michele Austin, et al. Diagnosis and Treatment of Vaginal Discharge Syndromes in Community Practice Settings, Clinical Infectious Diseases, , ciaa260, https://doi.org/10.1093/cid/ciaa260

## Malaria chemoprevention and management of severe anemia in children

Despite an increased risk for re-admission and death within six months after discharge of children hospitalised with severe anaemia in malaria endemic areas in Africa, no specific interventions cater for this period. A large multi-center, placebo-controlled trial in Kenya and Uganda studied the effect of three months of malaria chemoprevention on morbidity and mortality in children younger than five years of age. They found a significantly lower number of readmission or death events occurred in the chemoprevention group than the placebo group. The effect was however not sustained beyond the intervention period. The researchers concluded that, three months of postdischarge malaria chemoprevention with monthly dihydroartemisinin–piperaquine in children who had recently received treatment for severe anemia could prevent more deaths or readmissions for any reason after discharge than placebo in malaria endemic settings.

Kwambai TK, Dhabangi, et al. Malaria Chemoprevention in the Postdischarge Management of Severe Anemia. N Engl J Med. 2020 Dec 3;383(23):2242-2254. doi: 10.1056/NEJMoa2002820. PMID: 33264546.

# General

## Antibiotics are non-inferior to appendectomy for appendicitis treatment

COVID-19 has pushed the medical society to reconsider many aspects of healthcare delivery, including the role of antibiotics vis-à-vis appendectomy in the treatment of appendicitis. Appendectomy has for long been the standard treatment of appendicitis even though successful use of antibiotic therapy was reported more than 60 years ago.

A large non-inferiority randomised trial of 1552 adults was conducted at 25 centers in the U.S.A to compare antibiotic therapy (10-day course) with appendectomy in patients with appendicitis. The primary outcome was 30-day health status, and secondary outcomes: appendectomy in the antibiotics group and complications through 90 days. Data collected included presence or absence of an appendicolith. Antibiotics were found to be noninferior to appendectomy on the basis of results of a standard health-status measure. 3 in 10 participants in the antibiotics group underwent appendectomy by 90 days; presence of an appendicolith was associated with a higher risk for appendectomy and for complications.

CODA Collaborative, Flum, et al. A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis. N Engl J Med. 2020 Nov 12;383(20):1907-1919. doi: 10.1056/NEJMoa2014320. Epub 2020 Oct 5. PMID: 33017106.

## Psychological distress among TB patients in sub-Saharan Africa

Psychological distress, a not-so-rare comorbidity among patients with chronic diseases is often underdiagnosed and not effectively managed. In a recent systematic review researchers summarised available evidence on the prevalence of psychological distress among patients with tuberculosis (TB) in sub-Saharan Africa.They found a pooled prevalence of psychological distress among patients with TB in sub-Saharan Africa at 42.3% (95% CI 35.3–49.7). The pooled prevalence was as high as 61.1% in Cameroon, 47.7% in Ethiopia and 29.3% in South Africa. Female gender was associated with a higher prevalence. The researchers concluded that the prevalence of psychological distress among TB patients was high and recommended that TB programmes integrate psychiatry services into TB care to screen and manage psychologically distressed patients.

Duko B, Dana LM, Ayano G. Psychological distress among TB patients in sub-Saharan Africa. Int J Tuberc Lung Dis. 2020 Nov 1;24(11):1200-1204. doi: 10.5588/ijtld.20.0158. PMID: 33172528.

## Overweight and obesity among patients with type 2 diabetes mellitus in Uganda

Overweight and obesity are responsible for varied negative effects on health and are blamable for a significant proportion of non-communicable diseases, including type 2 diabetes mellitus. Researchers in Uganda recently evaluated the prevalence and risk factors of overweight and obesity among type 2 diabetes mellitus (T2DM) patients using a retrospective chart review. They found that among a sample of 1275 T2DM patients with a median age of 54 (IQR: 44–65) years, and a prevalence of hypertension of 69.6%; 349 (27%) were obese and 455 (36%) were overweight. Overweight/obesity were more prevalent among women, younger than 65years, on dual therapy, with peripheral neuropathy and hypertension belonging to a middle or high socioeconomic status. Authors concluded that "Overweight and obesity are high among T2DM patients in this population and may contribute significantly to poor outcomes of T2DM. Therefore, strategies to address this problem are urgently needed".

Tino S, et al. Prevalence and factors associated with overweight and obesity among patients with type 2 diabetes mellitus in Uganda-a descriptive retrospective study. BMJ Open. 2020 Nov 4

## Do behavioral interventions help people to quit cigarette smoking?

Smoking is a leading cause of morbidity and mortality worldwide. Quitting smoking can reverse much of the damage. Behavioral interventions used to help people quit smoking often have varied content and effectiveness. In a recent Cochrane review researchers summarised evidence on the effect of behavioral interventions intended to support smoking cessation, with focus on how delivery modes, the person delivering the intervention, the nature, focus and intensity of the intervention affect the likelihood of smoking cessation. From 312 studies involving 250,503 adult smokers, the authors found that counselling and guaranteed financial rewards were successful interventions whether or not pharmacotherapy was also used. Tailoring behavioural support to the person (s) trying to quit smoking slightly increased the number that stopped smoking. Increasing the intensity; frequency or duration of the support led to modest improvements. Findings on the role of other behavioral interventions like hypnotherapy, exercise and competitions were not as convincing.

Hartmann-Boyce J, et al. Behavioural interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD013229.

## Women physicians and promotion in academic medicine

A recent study was done to follow up findings from a landmark study in 2000 that found that women who graduated from U.S. medical schools from 1979 through 1997 were less likely to be promoted to upper faculty positions in academia compared to male colleagues. The researchers pooled data from the Association of American Medical Colleges on all medical school graduates from 1979 through 2013 with faculty data through 2018. They compared the percentages of women expected to be promoted based on the proportion of women in the graduating class, with actual percentages of women who were promoted. Using survival analysis they examined the differences between the early and later cohorts. 559,098 graduates from 134 U.S. medical schools were included in the study. Over the 35-year period, women physicians in academia were less likely than men to be promoted to the rank of associate or full professor or to be appointed to department chair, and the gap did not narrow over time.

Richter KP, Clark L, Wick JA, et al. Women Physicians and Promotion in Academic Medicine. The New England Journal of Medicine. 2020 Nov;383(22):2148-2157. DOI: 10.1056/nejmsa1916935

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